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FILE 'HOME' ENTERED AT 15:36:41 ON 31 JUL 2008

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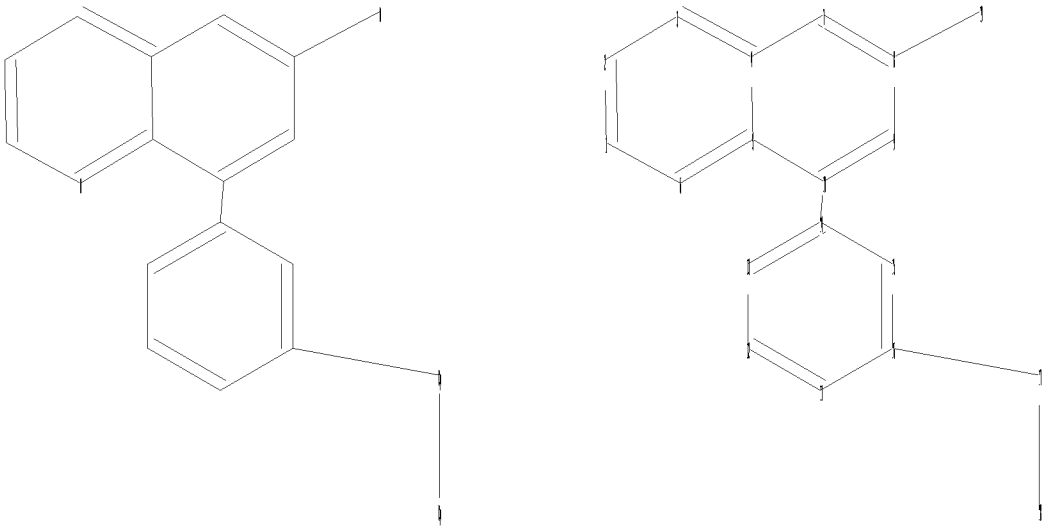
Uploading C:\Program Files\Stnexp\Queries\10554176.str



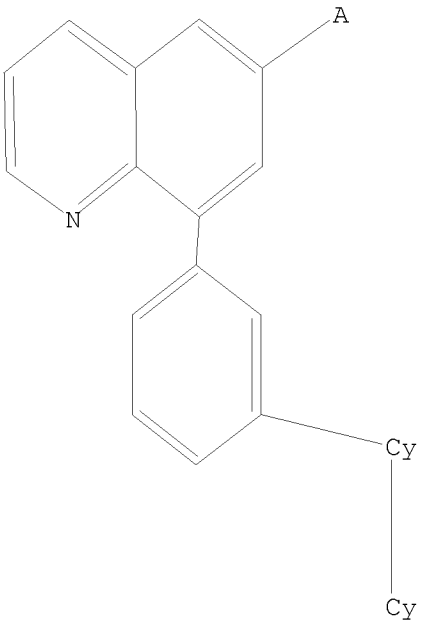
chain nodes :
17  18
ring nodes :
1  2  3  4  5  6  7  8  9  10  11  12  13  14  15  16
ring/chain nodes :
19
chain bonds :
8-19  10-14  16-17  17-18
ring bonds :
1-2  1-6  2-3  3-4  4-5  4-7  5-6  5-10  7-8  8-9  9-10  11-12  11-16  12-13  13-14
 14-15  15-16
exact/norm bonds :
8-19  16-17  17-18
exact bonds :
10-14
normalized bonds :
1-2  1-6  2-3  3-4  4-5  4-7  5-6  5-10  7-8  8-9  9-10  11-12  11-16  12-13  13-14
 14-15  15-16

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR




Structure attributes must be viewed using STN Express query preparation.

=> s l1 full
L3 201 SEA SSS FUL L1

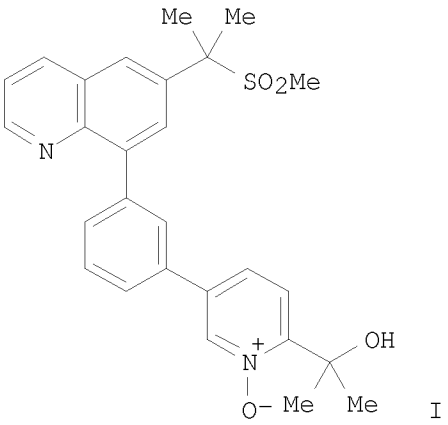
=> file ca

=> s l3
L4 4 L3

=> d ibib abs fhitstr 1-4

L4 ANSWER 1 OF 4 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 148:449430 CA
TITLE: Design, synthesis, and biological evaluation of 8-biarylquinolines: A novel class of PDE4 inhibitors
AUTHOR(S): Gallant, Michel; Chauret, Nathalie; Claveau, David; Day, Stephen; Deschenes, Denis; Dube, Daniel; Huang, Zheng; Lacombe, Patrick; Laliberte, France; Levesque,

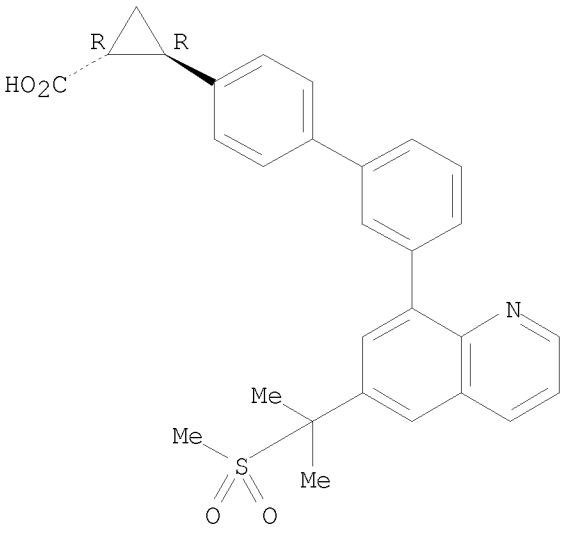
Jean-Francois; Liu, Susana; Macdonald, Dwight; Mancini, Joseph; Masson, Paul; Mastracchio, Anthony; Nicholson, Donald; Nicoll-Griffith, Deborah A.; Perrier, Helene; Salem, Myriam; Styhler, Angela; Young, Robert N.; Girard, Yves
CORPORATE SOURCE: Department of Medicinal Chemistry, Merck Frosst Center for Therapeutic Research, Pointe Claire-Dorval, QC, H9R 4P8, Can.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2008), 18(4), 1407-1412
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI




I

AB The structure-activity relationship of a novel series of 8-biarylquinolines, e.g., I, acting as type 4 phosphodiesterase (PDE4) inhibitors is described herein. Prototypical compds. from this series are potent and non-selective inhibitors of the four distinct PDE4 (IC50 < 10 nM) isoenzymes (A-D). In a human whole blood in vitro assay, they inhibit (IC50 < 0.5 μM) the LPS-induced release of the cytokine TNF-α. Optimized inhibitors were evaluated in vivo for efficacy in an ovalbumin-induced bronchoconstriction model in conscious guinea pigs. Their propensity to produce an emetic response was evaluated by performing pharmacokinetic studies in squirrel monkeys. This work has led to the identification of several compds. with excellent in vitro and in vivo profiles, including a good therapeutic window of efficacy over emesis.
IT 1019332-34-3P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation, phosphodiesterase 4 inhibitory activity, and SAR of biarylquinolines)
RN 1019332-34-3 CA
CN Cyclopropanecarboxylic acid, 2-[3'-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl][1,1'-biphenyl]-4-yl]-, (1R,2R)- (CA INDEX NAME)

Absolute stereochemistry.




REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 4 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 141:410960 CA
TITLE: Preparation of 8-(3-biaryl)phenylquinoline phosphodiesterase-4 inhibitors
INVENTOR(S): Dube, Daniel; Dube, Laurence; Gallant, Michel; Lacombe, Patrick; Deschenes, Denis; MacDonald, Dwight
PATENT ASSIGNEE(S): Merck Frosst Canada & Co., Can.
SOURCE: PCT Int. Appl., 129 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004096220 | A1 | 20041111 | WO 2004-CA622 | 20040427 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2004234190 | A1 | 20041111 | AU 2004-234190 | 20040427 |
| CA 2523336 | A1 | 20041111 | CA 2004-2523336 | 20040427 |
| EP 1635829 | A1 | 20060322 | EP 2004-729586 | 20040427 |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK

| | | | | | | |
|---|---|---|---|---|---|---|
| CN 1812787 | A | 20060802 | CN 2004-80018346 | | 20040427 |
| JP 2006524638 | T | 20061102 | JP 2006-504121 | | 20040427 |
| US 20060223850 | A1 | 20061005 | US 2005-554176 | | 20051021 |
| IN 2005DN04934 | A | 20070928 | IN 2005-DN4934 | | 20051027 |
| PRIORITY APPLN. INFO.: | | | US 2003-466542P | P | 20030430 |
| | | | WO 2004-CA622 | W | 20040427 |

OTHER SOURCE(S): MARPAT 141:410960
GI

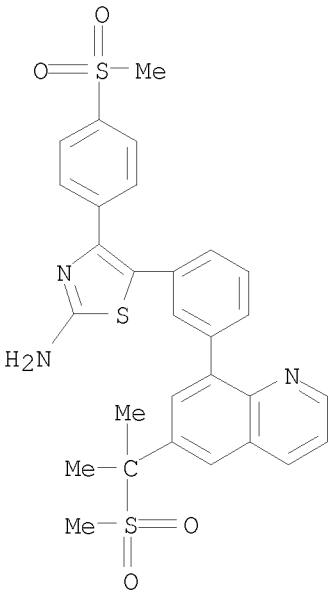
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title 8-phenylquinolines I [S1-S3 = H, OH, halo, alkyl, etc.; R1 = CO2aryl, CONHaryl, CONHheteroaryl, etc.; Ar1, Ar2 = (hetero)aryl or an N-oxide thereof; R2 = H, aryl, haloaryl, heterocyclyl, etc.; R3 = H, alkyl, hydroxyalkyl, etc.; R4 = H, halo, CN, alkyl, etc.] which are PDE4 inhibitors, were prepared E.g., a multi-step synthesis of II (no characterization data given for intermediates), which showed IC50 of 0.155 μM in LPS and FMLP-induced TNF-α and LTB4 assays in human whole blood, was given. The pharmaceutical compns. comprising the compound I are claimed.

IT 791630-50-7P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of 8-(3-biaryl)phenylquinoline phosphodiesterase-4 inhibitors)

RN 791630-50-7 CA

CN 2-Thiazolamine, 5-[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-4-[4-(methylsulfonyl)phenyl]- (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 4 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 140:59526 CA
TITLE: Preparation of 8-(biaryl)quinolines as PDE4 inhibitors
INVENTOR(S): Deschenes, Denis; Dube, Daniel; Dube, Laurence; Gallant, Michel; Girard, Yves; Lacombe, Patrick; MacDonald, Dwight
PATENT ASSIGNEE(S): Merck Frosst Canada & Co., Can.
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2004000814 | A1 | 20031231 | WO 2003-CA957 | | 20030623 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | | |
| CA 2490043 | A1 | 20031231 | CA 2003-2490043 | | 20030623 |
| AU 2003243870 | A1 | 20040106 | AU 2003-243870 | | 20030623 |
| EP 1517895 | A1 | 20050330 | EP 2003-760540 | | 20030623 |
| EP 1517895 | B1 | 20070314 | | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | | |
| JP 2006502104 | T | 20060119 | JP 2004-514482 | | 20030623 |
| AT 356808 | T | 20070415 | AT 2003-760540 | | 20030623 |
| ES 2282667 | T3 | 20071016 | ES 2003-760540 | | 20030623 |
| US 20050234238 | A1 | 20051020 | US 2004-517416 | | 20041208 |
| US 7153968 | B2 | 20061226 | | | |
| PRIORITY APPLN. INFO.: | | | US 2002-391364P | P | 20020625 |
| | | | US 2002-428313P | P | 20021122 |
| | | | WO 2003-CA957 | W | 20030623 |

OTHER SOURCE(S): MARPAT 140:59526
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [wherein A = C or N; X = Ph, pyridyl, pyrazinyl, thiaphenyl, quinolinyl, benzofuranyl, oxadiazolyl, diazolylpyridinyl, imidazolylpyridinyl, oxadiazolylphenyl, benzodioxolyl; R1 = H, halo, or (un)substituted alkanoyl, cyclo/alkyl, alkenyl; R2, R3 = independently H, halo, OH, CN, NO2, or dialkenyl/dicycloalkyl/alkyl, alkenyl, wide variety

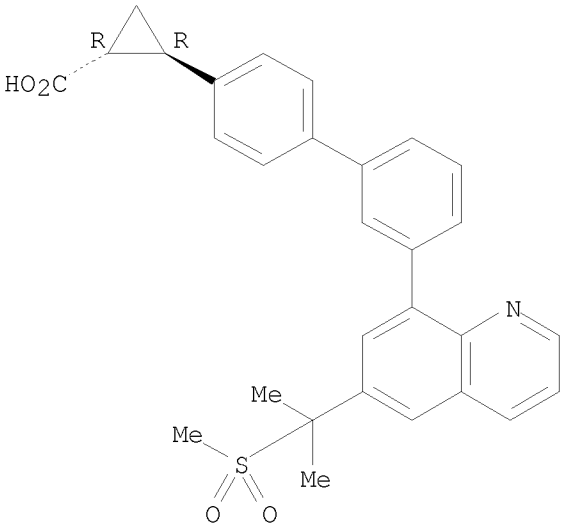
of C-containing and heteroat. groups and/or functional groups optionally linked by C1-4alkyl; R2 optionally forms a double bond with an adjoining bond; R4 = H, halo; any ring nitrogen optionally forms N-oxide and N-chloride; and pharmaceutically acceptable salts thereof] were prepared as phosphodiesterase IV (PDE4) inhibitors. For example, II was prepared by Suzuki cross-coupling of quinoline III with 2-bromo-3-chlorothiophene. One hundred fifty-five invention compds. suppressed PDE4 with IC50 values ranging from 36 μM to 0.005 μM in assays evaluating LPS- and FMLP-induced inhibition of tumor necrosis factor α (TNF-α) and leukotriene B4 (LTB4) in human whole blood. In a test measuring IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitized guinea pigs, administration of I resulted in a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes and effected less inflammatory lung damage. One hundred fifty-five invention compds. also inhibited the hydrolysis of cAMP to AMP by human recombinant phosphodiesterase IVa with IC50 values ranging from 160 nM to 0.086 nM. Thus, I and their pharmaceutical compns. are useful for the treatment or prevention of a variety of allergic, inflammatory, CNS, and other conditions (no data).

IT 638220-30-1P, trans-2-[3'-[6-[1-(Methylsulfonyl)-1-methylethyl]quinolin-8-yl]biphenyl-4-yl]cyclopropanecarboxylic acid
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(PDE4 inhibitor; preparation of 8-arylquinoline PDE4 inhibitors for treatment of a variety of allergic, inflammatory, CNS, and other conditions)

RN 638220-30-1 CA

CN Cyclopropanecarboxylic acid, 2-[3'-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl][1,1'-biphenyl]-4-yl]-, (1R,2R)-rel- (CA INDEX NAME)

Relative stereochemistry.




REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 4 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 138:73184 CA
TITLE: Preparation of substituted 8-arylquinoline phosphodiesterase-4 (PDE4) inhibitors
INVENTOR(S): Dube, Daniel; Girard, Yves; MacDonald, Dwight; Mastracchio, Anthony; Gallant, Michel; Lacombe, Patrick; Deschenes, Denis
PATENT ASSIGNEE(S): Merck Frosst Canada & Co., Can.
SOURCE: PCT Int. Appl., 204 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003002118 | A1 | 20030109 | WO 2002-CA953 | 20020626 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2450686 | A1 | 20030109 | CA 2002-2450686 | 20020626 |
| AU 2002344885 | A1 | 20030303 | AU 2002-344885 | 20020626 |
| AU 2002344885 | B2 | 20060629 | | |
| EP 1404330 | A1 | 20040407 | EP 2002-742600 | 20020626 |
| EP 1404330 | B1 | 20050601 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2005501822 | T | 20050120 | JP 2003-508357 | 20020626 |
| AT 296630 | T | 20050615 | AT 2002-742600 | 20020626 |
| ES 2242036 | T3 | 20051101 | ES 2002-742600 | 20020626 |
| US 20040162314 | A1 | 20040819 | US 2003-478791 | 20031125 |
| US 6919353 | B2 | 20050719 | | |

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|---|---|---|---|
| PRIORITY APPLN. INFO.: | US 2001-301220P | P | 20010627 |
| | US 2001-303472P | P | 20010706 |
| | WO 2002-CA953 | W | 20020626 |

OTHER SOURCE(S): MARPAT 138:73184
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

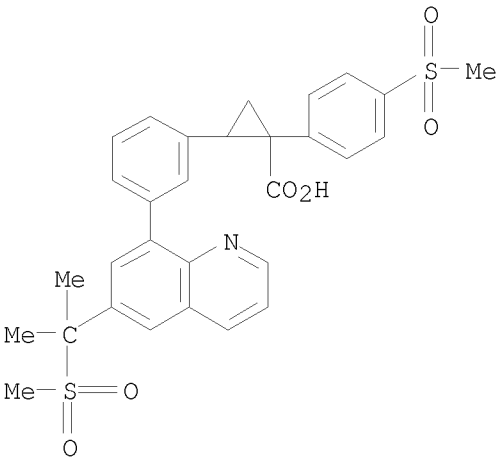
AB 8-Arylquinolines (shown as I; variables defined below; e.g. both enantiomers of 4-hydroxy-1-[3-[6-(1-methanesulfonyl-1-methylethyl)quinolin-8-yl]phenyl]-2-(4-methanesulfonylphenyl)-4-methylpentan-3-one) wherein the aryl group at the 8-position contains a meta two atom bridge to an optionally substituted Ph or pyridyl group, are PDE4 inhibitors useful to treat asthma, chronic bronchitis, chronic obstructive pulmonary disease, arthritis, respiratory distress syndrome, allergic rhinitis, neurogenic

inflammation, pain, rheumatoid arthritis, and other diseases. R1-R7 and Ar are as in claim 1. For I: Ar is Ph, pyridinone, pyridyl, or pyridyl N-oxide, optionally substituted with 1-5 independent -C1-6-alkyl, -OH, -CN, halogen, -CF3, -(C0-6-alkyl)-SOn-(C1-6-alkyl), -(C0-6-alkyl)-SOn-NH-(C1-6-alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms = O, S or N, wherein the 5-membered-ring is optionally substituted. R1 is H, halogen; or a -C1-6-alkyl, -cycloC3-6alkyl, -C1-6-alkenyl, -C0-4alkyl-C(O)-C0-4alkyl, -C1-6-alkoxy, aryl, heteroaryl, -CN, -heterocycloC3-6-alkyl, -amino, -C1-6-alkylamino, -(C1-6-alkyl)(C1-6-alkyl)amino, -C1-6-alkyl(oxy)C1-6-alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SOnNH(aryl), -SOnNH(heteroaryl), -SOnNH(C1-6-alkyl), -C(O)N(C0-6alkyl)(C0-6-alkyl), -NH-SOn-(C1-6-alkyl), -carbamoyl, -(C1-6-alkyl)-O-C(CN)dialkylamino, or -(C0-6-alkyl)-SOn-(C1-6-alkyl) group, wherein any of the groups is optionally substituted with = 1-5 substituents. R2, R3, R6, and R7 = H, halogen, hydroxy, -C1-6-alkyl, or -C1-6-alkoxy, wherein the alkyl and alkoxy are optionally substituted independently with 1-3 halogen or OH; R4 is H, halogen, -CN, Ph, oxadiazolyl, or -C(O)-O-C0-6alkyl, wherein the alkyl and latter three possibilities are optionally substituted. R5 is H, hydroxy, -CN; or a -C1-6-alkyl, -C(O)C1-6alkyl, -C(O)aryl, -C(O)pyridyl, -C(O)-O-C0-6-alkyl, -C(O)-C3-7-cycloalkyl, -C1-6-alkyl-C3-7cycloalkyl, -C1-6-alkyl(C3-7-cycloalkyl)2, -C1-6-alkylaryl, -C(O)-N(C0-6alkyl)2, -SOnaryl, -SOn-C1-6-alkyl, -SOn-C3-7-cycloalkyl, -SOn-N(C0-6-alkyl)2, -P(O)(C1-6-alkyl)2, -P(O)(C1-6-alkoxy)2, Ph, pyridyl, -SOnimidazolyl, -SOnthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms = O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted; or R5 and R6 form :O; or R6 and R3 form -CH2- or -O-; and n is 0-2. Although the methods of preparation are not claimed, >100 example prepns. are included. The IC50 values for PDE4 inhibition of Examples 1-113 generally are 0.02-26 μM as measured using LPS and FMLP-induced TNF-α and LTB4 assays in human whole blood. I were tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitized guinea pigs;. Administration of I (0.001-10 mg/kg i.p. or p.o.), up to three times during the 48 h following antigen challenge, lead to a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with I. Compds. which inhibit the hydrolysis of cAMP to AMP by the type-IV cAMP-specific phosphodiesterases were screened in a 96-well plate format; IC50 values of I generally ranged 0.1-25 nM.

IT 481680-95-9P, 2-[3-[6-(1-Methanesulfonyl-1-methylethyl)quinolin-8-yl]phenyl]-1-(4-methanesulfonylphenyl)cyclopropanecarboxylic acid
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of substituted 8-arylquinoline phosphodiesterase-4 (PDE4) inhibitors)

RN 481680-95-9 CA

CN Cyclopropanecarboxylic acid, 2-[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-1-[4-(methylsulfonyl)phenyl]- (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file marpat

=> s l1 full
L5 8 SEA SSS FUL L1

=> d ibib abs fqhit 1-8

L5 ANSWER 1 OF 8 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 148:472072 MARPAT
TITLE: Substituted pyrazinone derivatives as selective 2C-adrenoceptor antagonists for use as a medicine and their preparation
INVENTOR(S): Andres-Gil, Jose Ignacio; Alcazar-Vaca, Manuel Jesus; Linares De La Morena, Maria Lourdes; Martinez Gonzalez, Sonia; Oyarzabal Santamarina, Julen; Pastor-Fernandez, Joaquin; Vega-Ramiro, Juan Antonio; Delgado-Jimenez, Francisca; Drinkenburg, Wilhelmus Helena Ignatius Maria
PATENT ASSIGNEE(S): Janssen Pharmaceutica NV, Belg.
SOURCE: PCT Int. Appl., 74pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

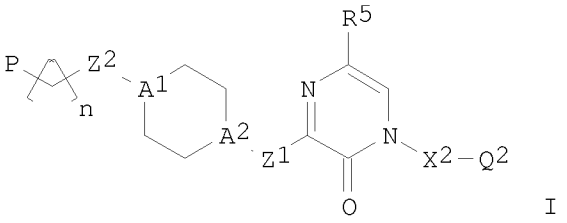
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2008043775 | A1 | 20080417 | WO 2007-EP60748 | 20071010 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,

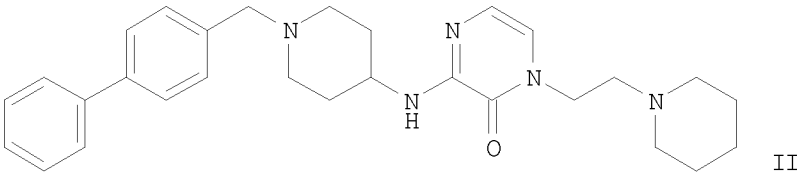
PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW,
GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: EP 2006-122173 20061012

GI



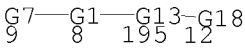

I



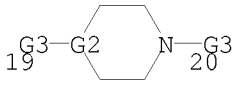

II

AB The invention concerns substituted pyrazinone derivs. according to the general formula I a pharmaceutically acceptable acid or base addition salt thereof, a stereochem. isomeric form thereof, an N-oxide form thereof or a quaternary ammonium salt thereof, having selective 2C-adrenoceptor antagonist activity. It further relates to their preparation, compns. comprising them and their use as a medicine. The compds. according to the invention are useful for the prevention and/or treatment of central nervous system disorders, mood disorders, anxiety disorders, stress-related disorders associated with depression and/or anxiety, cognitive disorders, personality disorders, schizoaffective disorders, Parkinson's disease, dementia of the Alzheimer's type, chronic pain conditions, neurodegenerative diseases, addiction disorders, mood disorders and sexual dysfunction. Compds. of formula I wherein A1 and A2 are independently N and C, with the proviso that not both A1 and A2 are C simultaneously; Z1, Z2 are independently a bond and NH and derivs.; n is 0, 1, 2, and 3; R5 is H and halo; P is Ph, biphenyl, 1,1-diphenylmethyl and benzyloxyphenyl; X2 is a bond, (un)saturated (un)substituted C1-8 hydrocarbon wherein one or more of the bivalent CH2 units may be replaced with bivalent Ph unit; Q2 is NH and derivs., nitrogen-heterocycle, OH and derivs., SH and derivs., SO2H and derivs., aryl, etc.; and their pharmaceutically acceptable acid and base addition salts, N-oxides and quaternary ammonium salts thereof, are claimed. Example compound II was prepared by N-alkylation of 3-(1-(biphenyl-4-ylmethyl)piperidin-4-yl)pyrazin-2-one with N-(2-chloroethyl)piperidine. All the invention compds. were evaluated for their 2C-adrenoceptor antagonistic activity (data given).

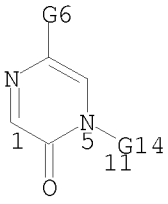
MSTR 1



G1 = 19-9 20-195



G2 = N
G3 = bond
G13 = 1-8 11-12



G14 = phenylene
G18 = quinolinyl (opt. substd. by G42)
G42 = Ph
Patent location: claim 1
Note: or pharmaceutically acceptable acid or base addition salts, N-oxides or quaternary ammonium salts
Note: additional derivatization also claimed

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 8 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 146:100694 MARPAT
TITLE: Preparation of piperidine derivatives as NMDA receptor antagonists
INVENTOR(S): Masui, Moriyasu; Matsumura, Akira
PATENT ASSIGNEE(S): Shionogi & Co., Ltd., Japan
SOURCE: PCT Int. Appl., 111pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006137465 | A1 | 20061228 | WO 2006-JP312466 | 20060622 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,

KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN,
MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU,
SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG,
US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM

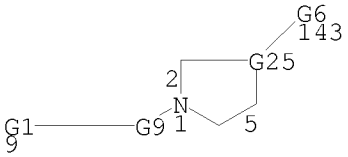
PRIORITY APPLN. INFO.: JP 2005-185100 20050624
JP 2005-309760 20051025

GI

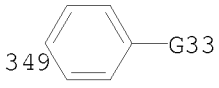
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [A1 = nitrogenated aromatic monocyclic group or nitrogenated aromatic fused-ring group which has at least one (un)protected hydroxy and/or amino and which may be substituted by other group, nitrogenated aromatic monocyclic group or nitrogenated aromatic fused-ring group which has -NH- in the ring and in which other ring-constituting atom may have substituent(s) (except (un)protected hydroxy and amino); A2 = (un)substituted aromatic cyclic hydrocarbon, (un)substituted aromatic heterocycle; R1 = H, hydroxy, acyloxy, etc.; R2 = H, hydroxy, alkyl; R1 and R2 may combine to form single bond; m = 0, 1; X = (un)substituted alkenylene, (un)substituted alkynylene, -CO(CR3R4)n-, etc.; R3, R4 = H, (un)substituted alkyl; n = 0-4; when m is 0, Y represents single bond, -O-, -S-, etc.; when m is 1, Y represents single bond, alkylene, alkenylene, etc.], pharmaceutically acceptable salts or solvates thereof were prepared For example, EDCI mediated amidation of 4-imidazolecarboxylic acid with compound II, e.g., prepared from 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride in 2 steps, afforded compound III [R = imidazol-4-yl] in 35% yield. In NMDA receptor (NR1/NR2B receptor) binding assays, the IC50 value of compound III [R = 2,3-dihydro-2-oxo-1H-benzimidazol-5-yl] was 0.002 μM. Compds. I are claimed useful as analgesics.

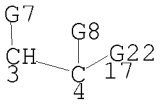
MSTR 1




G1 = quinolinyl (substd. by OH)
G6 = 349



G9 = phenylene
G22 = bond
G25 = 3-2 4-5 17-143



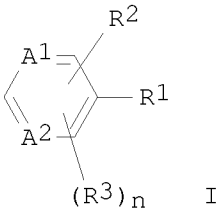

Patent location: claim 1
Note: substitution is restricted
Note: or pharmaceutically acceptable salts or solvates

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 8 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 144:610 MARPAT
TITLE: Phenol analogs for inducing hematopoietic stem cells and megakaryocytes
INVENTOR(S): Kashikura, Ikuo; Yoshizawa, Atsushi
PATENT ASSIGNEE(S): Ohtsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 16 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| JP 2005330204 | A | 20051202 | JP 2004-148779 | 20040519 |

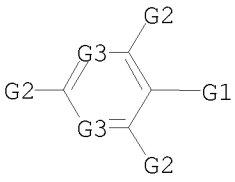
PRIORITY APPLN. INFO.: JP 2004-148779 20040519
GI



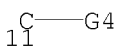

I

AB Phenol analogs (I; R1 = OH, Me, alkyl, alkoxy; R2 = (substituted) aryl or heteroaryl; R3 = H, halogen, alkyl, etc.; n = 2-4; A1, A2 = N, CH, C(R3)), including 4-(5-octylpyrimidin-2-yl)phenol, 4-[2-(4-butoxyphenyl)pyrimidin-5-yl]phenol, 2-(octylphenyl)pyrimidin-5-ol, 4-(5-octylpyridin-2-yl)phenol, 4-(6-pentylquinolin-2-yl)phenol or 4-[2-[4-(disiloxy)-2,3-difluorophenyl]pyrimidin-5-yl]phenol., are claimed for inducing hematopoietic stem cells and megakaryocytes for treatment of platelet diseases, anemia, leukemia, SLE, DIC, tumor, etc.

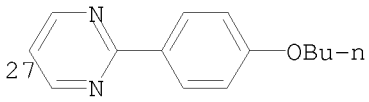
MSTR 1




G2 = (1) G5
G3 = 11




G5 = quinolinyl (opt. substd. by alkyl <containing 1-20 C>) / 27




Patent location: claim 1
Note: or salts

L5 ANSWER 4 OF 8 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 141:410960 MARPAT
TITLE: Preparation of 8-(3-biaryl)phenylquinoline phosphodiesterase-4 inhibitors
INVENTOR(S): Dube, Daniel; Dube, Laurence; Gallant, Michel; Lacombe, Patrick; Deschenes, Denis; MacDonald, Dwight
PATENT ASSIGNEE(S): Merck Frosst Canada & Co., Can.
SOURCE: PCT Int. Appl., 129 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004096220 | A1 | 20041111 | WO 2004-CA622 | 20040427 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,

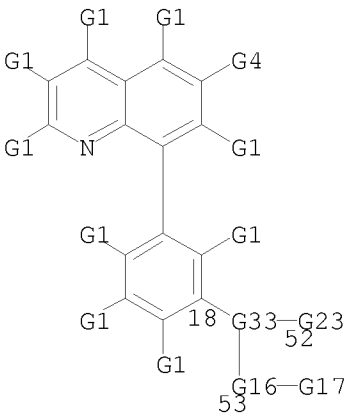
| | | | | |
|---|---|---|---|---|
| | SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| AU 2004234190 | A1 | 20041111 | AU 2004-234190 | 20040427 |
| CA 2523336 | A1 | 20041111 | CA 2004-2523336 | 20040427 |
| EP 1635829 | A1 | 20060322 | EP 2004-729586 | 20040427 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK | | | |
| CN 1812787 | A | 20060802 | CN 2004-80018346 | 20040427 |
| JP 2006524638 | T | 20061102 | JP 2006-504121 | 20040427 |
| US 20060223850 | A1 | 20061005 | US 2005-554176 | 20051021 |
| IN 2005DN04934 | A | 20070928 | IN 2005-DN4934 | 20051027 |
| PRIORITY APPLN. INFO.: | | | US 2003-466542P | 20030430 |
| | | | WO 2004-CA622 | 20040427 |

GI

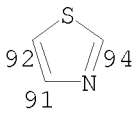
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title 8-phenylquinolines I [S1-S3 = H, OH, halo, alkyl, etc.; R1 = CO2aryl, CONHaryl, CONHheteroaryl, etc.; Ar1, Ar2 = (hetero)aryl or an N-oxide thereof; R2 = H, aryl, haloaryl, heterocyclyl, etc.; R3 = H, alkyl, hydroxyalkyl, etc.; R4 = H, halo, CN, alkyl, etc.] which are PDE4 inhibitors, were prepared E.g., a multi-step synthesis of II (no characterization data given for intermediates), which showed IC50 of 0.155 μM in LPS and FMLP-induced TNF-α and LTB4 assays in human whole blood, was given. The pharmaceutical compns. comprising the compound I are claimed.

MSTR 1




G4 = carbocycle <containing 3-6 C, 1-3 rings>
G16 = p-C6H4
G33 = 92-18 91-53 94-52




Patent location: claim 1
Note: or pharmaceutically acceptable salts

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 8 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 140:59526 MARPAT
TITLE: Preparation of 8-(biaryl)quinolines as PDE4 inhibitors
INVENTOR(S): Deschenes, Denis; Dube, Daniel; Dube, Laurence; Gallant, Michel; Girard, Yves; Lacombe, Patrick; MacDonald, Dwight
PATENT ASSIGNEE(S): Merck Frosst Canada & Co., Can.
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004000814 | A1 | 20031231 | WO 2003-CA957 | 20030623 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2490043 | A1 | 20031231 | CA 2003-2490043 | 20030623 |
| AU 2003243870 | A1 | 20040106 | AU 2003-243870 | 20030623 |
| EP 1517895 | A1 | 20050330 | EP 2003-760540 | 20030623 |
| EP 1517895 | B1 | 20070314 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| JP 2006502104 | T | 20060119 | JP 2004-514482 | 20030623 |
| AT 356808 | T | 20070415 | AT 2003-760540 | 20030623 |
| ES 2282667 | T3 | 20071016 | ES 2003-760540 | 20030623 |
| US 20050234238 | A1 | 20051020 | US 2004-517416 | 20041208 |
| US 7153968 | B2 | 20061226 | | |

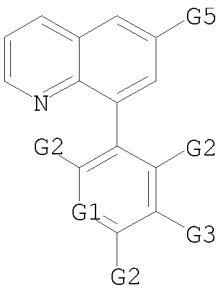
PRIORITY APPLN. INFO.: US 2002-391364P 20020625
US 2002-428313P 20021122
WO 2003-CA957 20030623

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [wherein A = C or N; X = Ph, pyridyl, pyrazinyl, thiaphenyl, quinolinyl, benzofuranyl, oxadiazolyl, diazolylpyridinyl, imidazolylpyridinyl, oxadiazolylphenyl, benzodioxolyl; R1 = H, halo, or (un)substituted alkanoyl, cyclo/alkyl, alkenyl; R2, R3 = independently H, halo, OH, CN, NO2, or dialkenyl/dicycloalkyl/alkyl, alkenyl, wide variety of C-containing and heteroat. groups and/or functional groups optionally linked by C1-4alkyl; R2 optionally forms a double bond with an adjoining bond; R4 = H, halo; any ring nitrogen optionally forms N-oxide and N-chloride; and pharmaceutically acceptable salts thereof] were prepared as phosphodiesterase IV (PDE4) inhibitors. For example, II was prepared by Suzuki cross-coupling of quinoline III with 2-bromo-3-chlorothiophene. One hundred fifty-five invention compds. suppressed PDE4 with IC50 values ranging from 36 μM to 0.005 μM in assays evaluating LPS- and FMLP-induced inhibition of tumor necrosis factor α (TNF-α) and leukotriene B4 (LTB4) in human whole blood. In a test measuring IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitized guinea pigs, administration of I resulted in a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes and effected less inflammatory lung damage. One hundred fifty-five invention compds. also inhibited the hydrolysis of cAMP to AMP by human recombinant phosphodiesterase IVa with IC50 values ranging from 160 nM to 0.086 nM. Thus, I and their pharmaceutical compns. are useful for the treatment or prevention of a variety of allergic, inflammatory, CNS, and other conditions (no data).

MSTR 1




G1 = 19

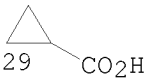
$_{19}C$—G2

G3 = 86

$_{86}p\text{-}C_6H_4$G13

G5 = cycloalkyl <containing 3-6 C>

(opt. substd. by (1-6) G6)
G13 = 129




Patent location: claim 1
Note: or pharmaceutically acceptable salts, N-oxides or N-chlorides

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 8 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 138:73184 MARPAT
TITLE: Preparation of substituted 8-arylquinoline phosphodiesterase-4 (PDE4) inhibitors
INVENTOR(S): Dube, Daniel; Girard, Yves; MacDonald, Dwight; Mastracchio, Anthony; Gallant, Michel; Lacombe, Patrick; Deschenes, Denis
PATENT ASSIGNEE(S): Merck Frosst Canada & Co., Can.
SOURCE: PCT Int. Appl., 204 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003002118 | A1 | 20030109 | WO 2002-CA953 | 20020626 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2450686 | A1 | 20030109 | CA 2002-2450686 | 20020626 |
| AU 2002344885 | A1 | 20030303 | AU 2002-344885 | 20020626 |
| AU 2002344885 | B2 | 20060629 | | |
| EP 1404330 | A1 | 20040407 | EP 2002-742600 | 20020626 |
| EP 1404330 | B1 | 20050601 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2005501822 | T | 20050120 | JP 2003-508357 | 20020626 |
| AT 296630 | T | 20050615 | AT 2002-742600 | 20020626 |
| ES 2242036 | T3 | 20051101 | ES 2002-742600 | 20020626 |
| US 20040162314 | A1 | 20040819 | US 2003-478791 | 20031125 |
| US 6919353 | B2 | 20050719 | | |

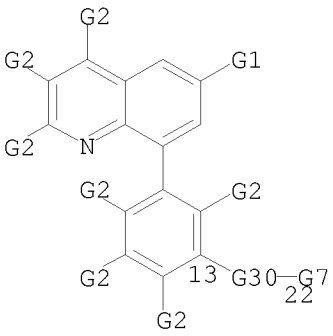
PRIORITY APPLN. INFO.: US 2001-301220P 20010627
US 2001-303472P 20010706
WO 2002-CA953 20020626

GI

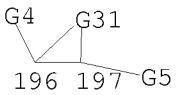
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB 8-Arylquinolines (shown as I; variables defined below; e.g. both enantiomers of 4-hydroxy-1-[3-[6-(1-methanesulfonyl-1-methylethyl)quinolin-8-yl]phenyl]-2-(4-methanesulfonylphenyl)-4-methylpentan-3-one) wherein the aryl group at the 8-position contains a meta two atom bridge to an optionally substituted Ph or pyridyl group, are PDE4 inhibitors useful to treat asthma, chronic bronchitis, chronic obstructive pulmonary disease, arthritis, respiratory distress syndrome, allergic rhinitis, neurogenic inflammation, pain, rheumatoid arthritis, and other diseases. R1-R7 and Ar are as in claim 1. For I: Ar is Ph, pyridinone, pyridyl, or pyridyl N-oxide, optionally substituted with 1-5 independent -C1-6-alkyl, -OH, -CN, halogen, -CF3, -(C0-6-alkyl)-SOn-(C1-6-alkyl), -(C0-6-alkyl)-SOn-NH-(C1-6-alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms = O, S or N, wherein the 5-membered-ring is optionally substituted. R1 is H, halogen; or a -C1-6-alkyl, -cycloC3-6alkyl, -C1-6-alkenyl, -C0-4alkyl-C(O)-C0-4alkyl, -C1-6-alkoxy, aryl, heteroaryl, -CN, -heterocycloC3-6-alkyl, -amino, -C1-6-alkylamino, -(C1-6-alkyl)(C1-6-alkyl)amino, -C1-6-alkyl(oxy)C1-6-alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SOnNH(aryl), -SOnNH(heteroaryl), -SOnNH(C1-6-alkyl), -C(O)N(C0-6alkyl)(C0-6-alkyl), -NH-SOn-(C1-6-alkyl), -carbamoyl, -(C1-6-alkyl)-O-C(CN)dialkylamino, or -(C0-6-alkyl)-SOn-(C1-6-alkyl) group, wherein any of the groups is optionally substituted with = 1-5 substituents. R2, R3, R6, and R7 = H, halogen, hydroxy, -C1-6-alkyl, or -C1-6-alkoxy, wherein the alkyl and alkoxy are optionally substituted independently with 1-3 halogen or OH; R4 is H, halogen, -CN, Ph, oxadiazolyl, or -C(O)-O-C0-6alkyl, wherein the alkyl and latter three possibilities are optionally substituted. R5 is H, hydroxy, -CN; or a -C1-6-alkyl, -C(O)C1-6alkyl, -C(O)aryl, -C(O)pyridyl, -C(O)-O-C0-6-alkyl, -C(O)-C3-7-cycloalkyl, -C1-6-alkyl-C3-7cycloalkyl, -C1-6-alkyl(C3-7-cycloalkyl)2, -C1-6-alkylaryl, -C(O)-N(C0-6alkyl)2, -SOnaryl, -SOn-C1-6-alkyl, -SOn-C3-7-cycloalkyl, -SOn-N(C0-6-alkyl)2, -P(O)(C1-6-alkyl)2, -P(O)(C1-6-alkoxy)2, Ph, pyridyl, -SOnimidazolyl, -SOnthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms = O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted; or R5 and R6 form :O; or R6 and R3 form -CH2- or -O-; and n is 0-2. Although the methods of preparation are not claimed, >100 example prepns. are included. The IC50 values for PDE4 inhibition of Examples 1-113 generally are 0.02-26 μM as measured using LPS and FMLP-induced TNF-α and LTB4 assays in human whole blood. I were tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitized guinea pigs;. Administration of I (0.001-10 mg/kg i.p. or p.o.), up to three times during the 48 h following antigen challenge, lead to a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with I. Compds. which inhibit the hydrolysis of cAMP to AMP by the type-IV cAMP-specific phosphodiesterases were screened in a 96-well plate format; IC50 values of I generally ranged 0.1-25 nM.

MSTR 1




G1 = carbocycle <containing 3-6 C, mono- or polycyclic>
(opt. substd.)
G4 = Ph (opt. substd. by (1-3) G15)
G30 = 196-13 197-22




G31 = O
Patent location: claim 1
Note: or pharmaceutically acceptable salts

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 8 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 135:288703 MARPAT
TITLE: 3-Cyanoquinolines, 3-cyano-1,6-naphthyridines, and 3-cyano-1,7-naphthyridines as protein kinase inhibitors
INVENTOR(S): Boschelli, Diane Harris; Wang, Yanong; Boschelli, Frank Charles; Berger, Dan Maarten; Zhang, Nan; Powell, Dennis William; Ye, Fei; Yamashita, Ayako; Demorin, Frenel Fils; Wu, Biqi; Tsou, Hwei-ru; Overbeek-klumpers, Elsebe Geraldine; Wissner, Allan
PATENT ASSIGNEE(S): American Home Products Corporation, USA
SOURCE: PCT Int. Appl., 448 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001072711 | A1 | 20011004 | WO 2001-US9966 | 20010328 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,

RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

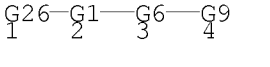
| | | | | |
|---|---|---|---|---|
| CA 2404662 | A1 | 20011004 | CA 2001-2404662 | 20010328 |
| EP 1268431 | A1 | 20030102 | EP 2001-924407 | 20010328 |
| EP 1268431 | B1 | 20070829 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| BR 2001009650 | A | 20030422 | BR 2001-9650 | 20010328 |
| JP 2003528857 | T | 20030930 | JP 2001-570624 | 20010328 |
| AT 371647 | T | 20070915 | AT 2001-924407 | 20010328 |
| ES 2291311 | T3 | 20080301 | ES 2001-924407 | 20010328 |
| MX 2002PA09439 | A | 20030224 | MX 2002-PA9439 | 20020926 |
| PRIORITY APPLN. INFO.: | | | US 2000-535843 | 20000328 |
| | | | WO 2001-US9966 | 20010328 |

GI

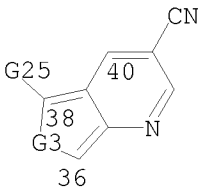
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [X = N(H) or substituted derivs., O, SO0-2; n = 0-1; A = divalent (un)substituted alkyl, C(O), C(O)-alkyl, alkyl-C(O), cycloalkyl, or absent; T, Z = C, N provided that both T and Z are not N; R1 = cycloalkyl, 5-6 atom (hetero)aryl ring containing 0-4 heteroatoms, 8-20 atom bicyclic heteroaryl ring containing 1-4 heteroatoms, etc.; R2a-c = H, aryl, CH2-aryl, O-aryl, SO0-2-aryl, NO2, SH, etc.; R3 = alkenyl, alkynyl, (hetero)aryl; R4 = (un)substituted alkyl, alkenyl, alkynyl, (hetero)aryl] were prepared Over 500 synthetic examples were disclosed, including some combinatorial prepns., and addnl. reference examples. E.g., 4-[(4-bromo-2-thienyl)methyl]morpholine reacted with bis(pinacolato)diboron [DMSO, PdCl2(dppf), KOAc] to give dioxaborolane II. II was coupled to 7-bromo-4-[3-chloro-4-[(1-methyl-1H-imidazol-2-yl)sulfanyl]anilino]-3-quinolinecarbonitrile [preparation given; diglyme, Pd(PPh3)4, NaHCO3] to yield invention compound III as a yellow solid after purification III had IC50 = 6.0 nM for Raf1 kinase and inhibited the human adenocarcinoma CaCo-2 cell line with IC50 = 1.9, 0.78 (2 trials). I are useful as antineoplastic agents, and in the treatment of osteoporosis and polycystic kidney disease.

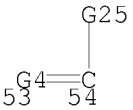
MSTR 1



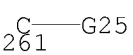

G1 = 36-1 40-3



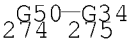

G3 = 53-38 54-36



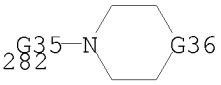

G4 = 261



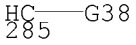

G25 = OMe
G26 = 274



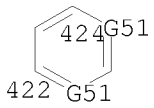

G34 = 282




G35 = (0-5) CH2
G36 = 285




G38 = pyrrolidino
G50 = 422-2 424-275




G51 = CH
Patent location: claim 1
Note: substitution is restricted

Note: or pharmaceutically acceptable salts

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 8 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 125:142750 MARPAT
TITLE: Polyarylcarbamoylaza- and -carbamoylalkanedioic acids as squalene synthase inhibitors
INVENTOR(S): Pauls, Henry W.; Choi, Yong-Mi; Studt, Robert W.; Maguire, Martin P.; Spada, Alfred P.; Cha, Don D.
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9618615 | A1 | 19960620 | WO 1995-US15364 | 19951129 |
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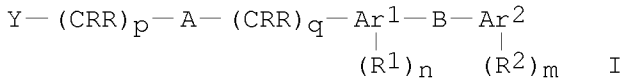
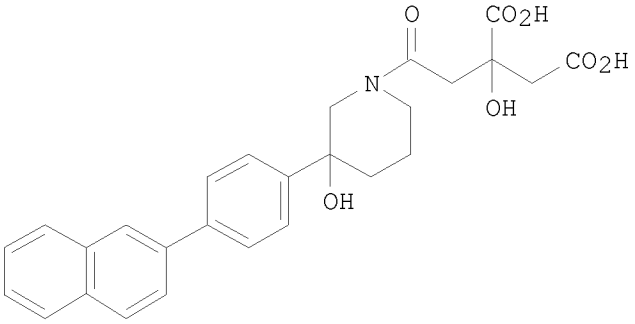
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5556990 | A | 19960917 | US 1994-357481 | 19941216 |
| CA 2207429 | A1 | 19960620 | CA 1995-2207429 | 19951129 |
| AU 9643698 | A | 19960703 | AU 1996-43698 | 19951129 |
| AU 695852 | B2 | 19980827 | | |
| EP 801644 | A1 | 19971022 | EP 1995-942489 | 19951129 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE | | | | |
| JP 10511084 | T | 19981027 | JP 1995-518973 | 19951129 |
| PRIORITY APPLN. INFO.: | | | US 1994-357481 | 19941216 |
| | | | WO 1995-US15364 | 19951129 |

GI



I



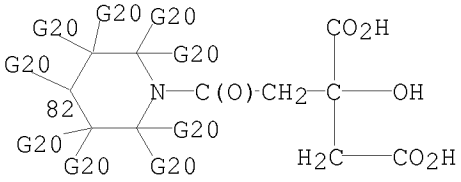
II

AB This invention relates to a class of novel dicarboxy amide derivs. of lipophilic amines I wherein: A is O, S, NR, SO, SO2, or a bond; B is (CRR)1-2, O, S, NR, SO, SO2, RC:CR, C.tplbond.C, CO, or a bond; Y is, e.g., RNZ(CRR)dCRR, N-Z-piperidyl, where Z is COWCR7[(CR3R4)fCO2R][(CR5R6)gCO2R]; W is a bond, (CRR)h, or NR; R = H, alkyl; R1, R2 are independently H, alkyl, alkoxy, OH, halo, haloalkyl, Ph; R3-R6 are independently H, alkyl; R7 is H, NRR, or OH and when W is (CRR)h then R7 is OH; one of R3-R7 is OH; Ar1 and Ar2 are independently a mono- or diaryl or heteroaryl; p and q are independently 0-3; p + q is 0-4; d is 0-3; p + q + d is 1-3; f is 0-2; g is 0-2; h is 1-2; m and n are independently 0-2; which exhibit squalene synthase inhibition properties. Compds. of this invention reduce levels of serum cholesterol in the body without significantly reducing mevalonic metabolite synthesis. This invention relates also to pharmacol. compns. and method of treatment for lowering serum cholesterol levels using the compds. of this invention. Thus, e.g., coupling of prepared intermediates 3-hydroxy-3-(4-naphth-2-ylphenyl)piperidine with 3-hydroxy-3,4-bis(ethoxycarbonyl)butanoic acid afforded the diester intermediate which was hydrolyzed to the diaryl carbamoyl alkanedioic acid II which exhibited inhibition of squalene synthase with IC50 = 27 nM.

MSTR 1B

G1—G16—G18

G1 = 82



```
G12    = Ph
G16    = phenylene (opt. substd. by (1-2) G12)
G18    = quinolinyl (opt. substd. by (1-2) G12)
G20    = Ph
Derivative:                or pharmaceutically acceptable salts
Patent location:           claim 1
Note:                      substitution is restricted
Stereochemistry:           stereoisomers, enantiomers, diastereoisomers, and
                           racemic mixtures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L2           13 S L1 SAM
L3          201 S L1 FULL

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L4            4 S L3

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L5            8 S L1 FULL

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